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Facile Synthesis of 2-Substituted 1,2-Dihydro-1-naphthols and 2-Substituted 1-Naphthols

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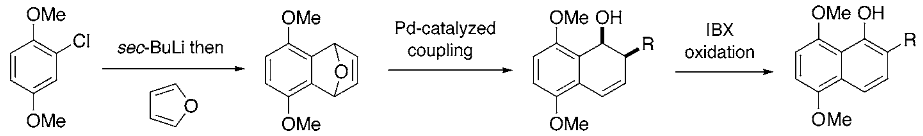
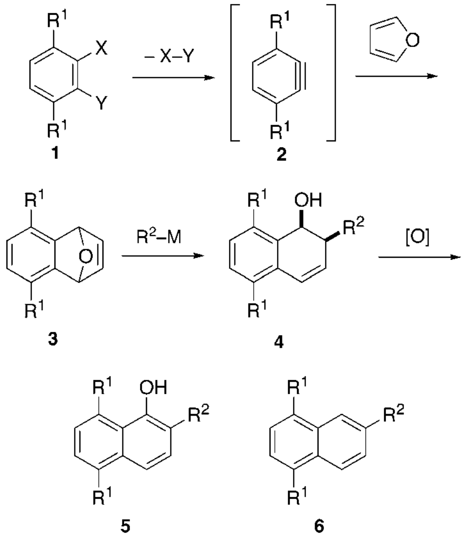
ABSTRACT



The palladium-catalyzed ring opening of dimethoxy oxabenzonorbornadiene with aryl or vinyl halides occurred under very mild conditions to give substituted 1,2-dihydronaphthols that were oxidized with IBX to furnish substituted naphthols in excellent overall yields.

In the context of developing general synthetic approaches to the various groups of *C*-aryl glycosides,[1] it occurred to us that suitable modification of some of the chemistry we had discovered would lead to a facile and efficient entry to 1,2-dihydro-1-naphthols and 1-naphthols from benzenoid precursors according to Scheme 1. The key elements of the methodology would entail the Diels−Alder reaction of a benzyne **2**, which would be generated in situ from **1**, with furan to give **3**. Subsequent ring opening of **3** would then provide the substituted dihydro-1-naphthol **4** that would be transformed into the substituted 1-naphthol **5**. Although numerous procedures for inducing the ring opening of oxabenzonorbornadienes **3** to give **4** are known,[2−10] most are subject to one or more limitations involving efficiency, generality, or ease of application. Related to the present work, Cheng and co-workers found that the Pd(0)-catalyzed reaction of electron-deficient aryl halides with **3** gave primarily

Scheme 1. General Strategy for Synthesis of 2-Substituted 1,2-Dihydro-1-naphthols and 2-Substituted 1-Naphthols



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(1) (a) Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937. (b) Apsel, B.; Bender, J.; Escobar, M.; Kaelin, D. E., Jr; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075. (c) Kaelin, D. E., Jr.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994.

(2) For reviews, see: (a) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(3) Arylboronic acids: (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, *4*, 390. (b) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695.

(4) Dialkylzincs: (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (c) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703.

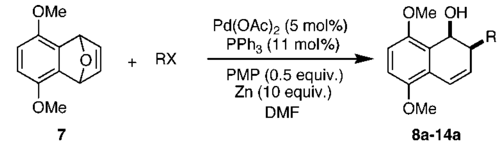
(5) Alkylzinc halides: Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679.

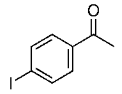
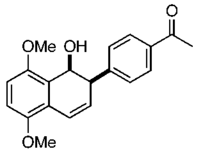
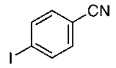
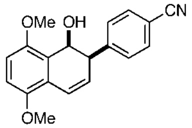
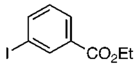
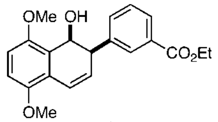
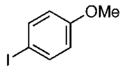
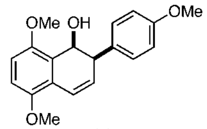
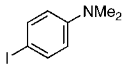
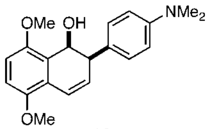
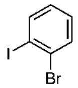
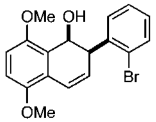
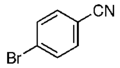
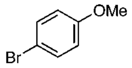
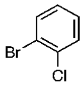
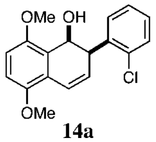
10.1021/ol048517t CCC: $27.50

the dehydration products **6** rather than the desired ring-opened products **4**.[9a] Moreover, we noted in previous work that the oxidation of compounds of the general formula **4** (R1 = OMe) was difficult, with dehydration to give **6** being a significant and deleterious side reaction.[1a] Hence, general methodology for the synthesis of the naphthol derivatives **4** and **5** from benzene derivatives according to the strategy outlined in Scheme 1 was lacking. Herein we report an effective solution to this important problem.

On the basis of our previous experience with ring opening reactions of oxabenzonorbornadienes, it occurred to us that altering the reaction conditions originally set forth by Cheng[9] constituted a useful point of embarkation for the present investigation. Clearly milder conditions would be required if we were to be successful in our venture of using electron-deficient aryl halides in the ring opening reaction. After extensive screening of various combinations of palladium and nickel precatalysts, solvents, amine bases, and temperatures, we eventually discovered that the combination of Pd(OAc)$_2$, PPh$_3$, 1,2,2,6,6-pentamethyl piperidine (PMP), and Zn in DMF was highly effective in promoting this transformation. PMP, which has been previously employed to advantage in Heck reactions,[11] was superior to Et$_3$N and inorganic bases. THF, acetonitrile, and toluene were all inferior to DMF as solvent. Thus, treatment of the dimethoxy oxabenzonorbornadiene **7**[12] with *p*-iodoacetophenone (1.2 equiv) in the presence of Pd(OAc)$_2$ (0.05 equiv), PPh$_3$ (0.11 equiv), Zn (10 equiv), and PMP (0.5 equiv) in DMF at room temperature afforded the *cis*-1,2-dihydronaphthol **8a** in 95% yield accompanied by only trace amounts of a naphthalene arising from dehydration of **8a** (Table 1, entry 1). Under similar conditions, a series of other electron-rich and electron-deficient aryl iodides were found to serve as excellent partners in the ring opening reaction (entries 2−6). Because no trans isomer was detected in these reactions by ^{1}H NMR, the carbopalladation of **7** appears to be a highly exo-selective addition. Remarkably, electron-withdrawing or electron-donating substituted aryl bromides also underwent facile reaction with **7**, albeit at higher temperatures, to provide the expected ring opened products **9a**, **11a**, and **14a** (entries 7−9). Under the mild conditions enabled by this catalyst system, very little dehydration of the dihydronaphthols was observed.

Table 1. Pd-Catalyzed Ring Opening of Oxabenzonorbornadiene **7** with Aryl Halides[a]



entry	RX	product	yield(%)[b]
1[c]		 **8a**	95
2[c]		 **9a**	90
3[c]		 **10a**	92
4[d]		 **11a**	90
5[d]		 **12a**	83
6[d]		 **13a**	94
7[e,f]		**9a**	73
8[e,g]		**11a**	73
9[e,h]		 **14a**	90

[a] Conditions: 0.05 M **7**, 1.2 equiv of RX. [b] Isolated yield of product after chromatography. [c] Room temperature. [d] 35 °C. [e] Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %). [f] 45 °C. [g] 65 °C. [h] 60 °C.

We recently reported that glycal-substituted *cis*-1,2-dihydronaphthols could be oxidized to the corresponding *C*-aryl glycosides using recrystallized DDQ.[1a,b] However, oxidation of **11a** under these conditions yielded only trace amounts of the desired 2-aryl-1-naphthol **11b**. Driven by this failure, we then examined numerous oxidants to effect this transformation,[13] but the naphthol **11b** was invariably isolated

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(6) Organolithiums: (a) Caple, R.; Chen, G. M. S.; Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874. (b) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954. (c) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442.

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(8) Phenylstannanes: Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 477.

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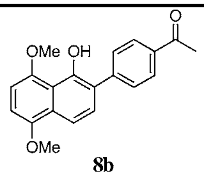
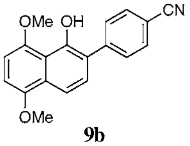
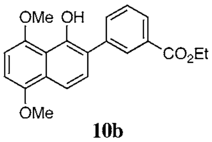
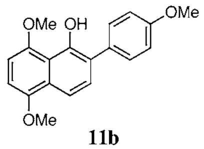
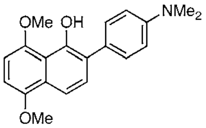
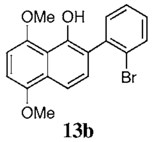
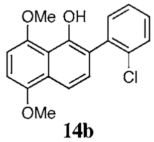
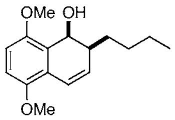
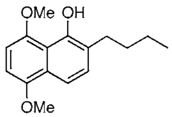
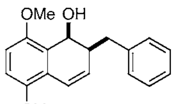
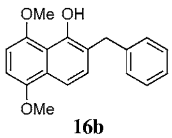
(10) Organic triflates: Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051.

(11) For a discussion of the use of different bases for Heck reactions, see: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

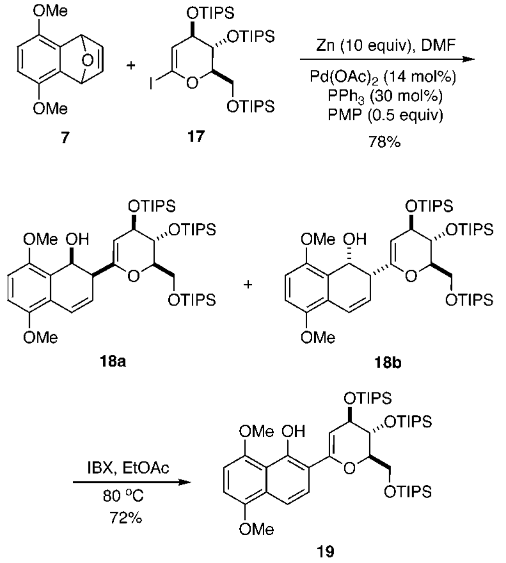
(12) Brimble, M. A.; Duncalf, L. J.; Phythian, S. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1399.

Table 2. Oxidation of 2-Substituted 1,2-Dihydro-1-naphthols with IBX[a]

entry	alcohol	product	yield(%)[b]
1	**8a**	 **8b**	88
2[c]	**9a**	 **9b**	76
3[c]	**10a**	 **10b**	81
4	**11a**	 **11b**	94
5	**12a**	 **12b**	80
6	**13a**	 **13b**	92
7	**14a**	 **14b**	84
8[d]	 **15a**[e]	 **15b**	85
9[d]	 **16a**[f]	 **16b**	91

[a] Reaction conditions: IBX (3 equiv) in EtOAc at 60 °C. [b] Isolated yield of product after chromatography. [c] Using acetone as solvent, 40 °C. [d] 80 °C. [e] Formed in 98% yield by ring opening of **7** with *n*-butyllithium (5 equiv) in the presence of TMEDA (2 equiv) in THF at −78 °C. [f] Formed in 87% yield by ring opening of **7** with benzyllithium (2.5 equiv) in the presence of TMEDA (2 equiv) in THF at 0 °C.

Scheme 2. Synthesis of *C*-Aryl Glycosides



in poor yield in combination with the dehydration product and/or recovered starting material and several unidentified products. We eventually found that oxidation of **11a** with IBX in ethyl acetate or acetone[14] gave naphthol **11b** in excellent yield under mild conditions; treating alcohol **11a** with IBX (3 equiv) in EtOAc at 60 °C for 14 h afforded naphthol in 94% yield (Table 2, entry 4). IBX was then employed to oxidize the dihydronaphthols **8a**−**10a** and **12a**−**16a** to afford the corresponding naphthols **8b**−**10b** and **12b**−**16b** in excellent yields and with little dehydration (Table 2).

In connection with our ongoing efforts directed toward the synthesis of *C*-aryl glycosides, we applied these new ring opening and oxidation protocols to an improved route to **19**.[1a] Thus, reaction of **7** with glycal iodide **17** provided a mixture (4:1) of diastereomeric *cis*-dihydronaphthols **18a** and **18b**; the relative stereochemistry of the major isomer was not established (Scheme 2). Subsequent oxidation of this mixture with IBX provided *C*-aryl glycoside **19** in a superior overall yield with no dehydration of the intermediate dihydronaphthols **18a** and **18b** being observed.

In summary, we have developed a general and efficient method for the synthesis of 2-substituted 1,2-dihydro-1-naphthols and 2-substituted 1-naphthols from benzene derivatives by sequential palladium-catalyzed ring opening of oxabenzonorbornadienes with aryl or vinyl halides followed

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(13) Oxidation of **11a** with Dess−Martin periodinane, PCC, Swern, Pd$(OAc)_2$/pyridine/O_2/toluene, Pd$(OAc)_2$/$NaHCO_3$/O_2/DMSO, Pd$(PPh_3)_4$/PhBr/DMF/K_2CO_3 or NaH, and IBX/H_2O/acetone/cyclodextrin failed to produce the desired naphthol **11b** in significant yield. These oxidants typically led to formation of the dehydration product as the major product. Other mild oxidation conditions, such as TPAP, DMSO/NEt_3/py-SO_3, MnO_2, or *p*-chloranil, only provided recovered starting material. In addition, oxidation of **11a** with Pd(nbd)Cl_2/spartein/O_2, NCS/DMS/NEt_3, and DMDO provided only trace yield of **11b** together with several unidentified products and/or recovered starting material.

(14) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

by oxidation with IBX. The method is applicable to aryl halides with both electron-withdrawing and -donating groups. Efforts are currently underway to expand the scope of this strategy, and the results of these investigations will be reported in due course.

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Supporting Information Available: Characterization data and copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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